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Review

The emergence of biological homochirality

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The homochirality of biological molecules is one of the basic mysteries of biogenesis. The predominance of L-amino acids and D-hydrocarbons in living matter stands in contrast to the chemical principle of symmetry between enantiomers. An answer to the puzzle needs to include a plausible explanation of how the natural racemic balance was initially tipped in favor of one enantiomer and how the initial tiny excess was amplified to significant levels. It is also necessary to consider how the imbalance was sustained from returning to a thermodynamic equilibrium. This is a review of the main concepts and observations, followed by a brief discussion.

Keywords: symmetry breaking, parity violation, homochirality, monochirality, biological enantiomers, racemic compounds, conglomerates, kryptoracemate

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Abbreviations: CD, circular dichroism; TC, isothermal titration calorimetry; PVED, parity violating energy difference

The processes by which life had arisen from nonliving matter are almost certainly beyond our cognitive horizon, but we can consider the milestone events that needed to occur at the onset of life's evolution. One of them is the selection from the "primordial soup" of the enantiomers that henceforth have determined life on Earth.

The biological predominance of L-amino acids and D-sugars needs to be explained because it stands in contrast to the chemical principle of equivalence between enantiomers (Fig. 1). As a rule, the chemical synthesis of chiral compounds from nonchiral components results in a balanced mixture of enantiomers, known as racemate. This natural balance was evidently broken in the early days of life's evolution on Earth, resulting in the observed homochirality of biological molecules. By an unknown mechanism, one enantiomer outweighed its symmetric counterpart and then the initial imbalance was somehow enhanced, leading to the near exclusion of the other enantiomer. The predominance of L-amino acids and D-sugars is found in all known life forms, indicating that the initial enantioselectivity and the following enantioenhancement must have occurred at the earliest stages of life's evolution.

Several models have been proposed of how the chemical symmetry was broken. They use physical factors, both internal and external to the molecules, probabilistic effects that could break the symmetry and chemical processes that could drive chiral resolution.

The purpose of this paper is to survey only the main concepts and observations concerning enantioselectivity, and to consider how any emerging imbalance could be sustained from returning to thermodynamic equilibrium.

Deterministic models rely on symmetry-breaking forces in nature. The natural place to look for the origin of chiral bias is the very fabric of nature, which is known to contain a chiral component. One of the fundamental forces, the weak interactions, violate parity-symmetry (Wu *et al.*, 1957). Weak interactions occur in the atomic nuclei, but their effect permeates the electronic structure, modifying its wave function and energy. Being chiral, the weak interactions should stabilize one enantiomer and destabilize the other (Fig. 2). This can possibly be detected, but there are no conclusive observations of such an effect (Avalos *et al.*, 2000). Initial theoretical calculations yielded energies of approximately 10^{-14} J/mol for simple amino acids or sugars (Tranter, 1985; Tranter, 1987; Mason & Tranter, 1985). Subsequent calculations on simple molecules indicated that the effect could be as high as 10^{-11} J/mol (Quack, 2002). This is taken as a free energy difference and corresponds to an excess of 10^{6}-10^{9} molecules of one enantiomer in a mole of the racemic mixture, correlating to one molecule in ~10^{15}–10^{18} (Ava-

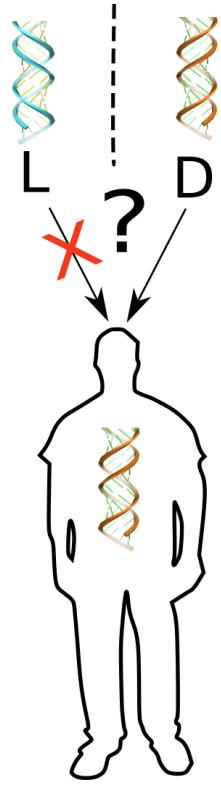

Figure 1. Biological molecules have distinct chirality.
Nucleic acids and carbohydrates (sugars) have the D-configuration, while proteins have the L-configuration.

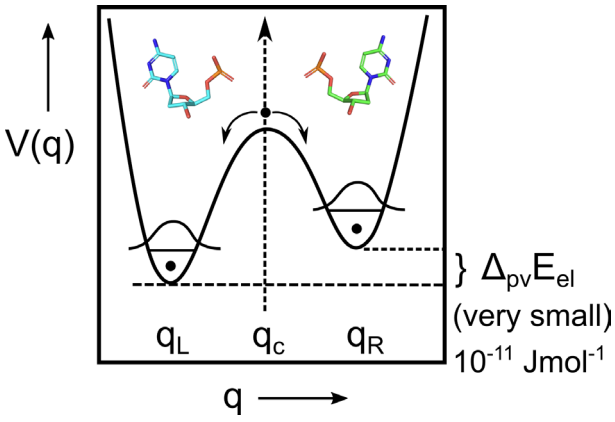

Figure 2. Parity violating weak interactions break the mirror symmetry in nature.
This is effectively demonstrated in particle physics but their effect on the stability of small chiral molecules has only been estimated. The electronic potential profile for enantiomers is not symmetric but the predicted value of the parity violating energy difference (PVED, $\Delta_{pv}E_{el}$) is very small, amounting to 10^{-11} J mol^{-1}.

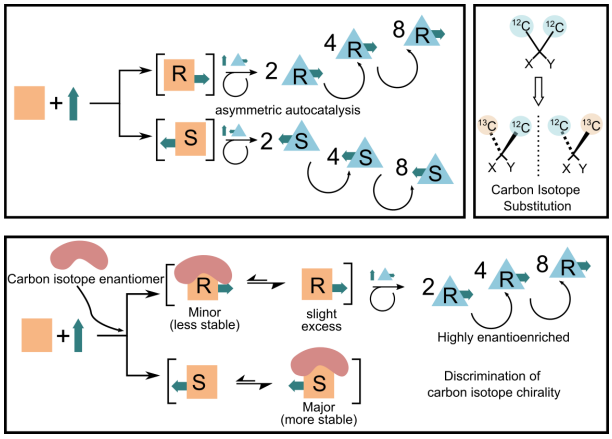

Figure 3. Scheme illustrating an autocatalytic reaction, with an "isotope enantiomer" stimulating the production of one enantiomer and inhibiting the other.

los *et al.*, 2000). These amounts are orders of magnitude below the statistical noise level; the Poisson noise is 8×10^{11} molecules per mole (Quack, 2012). To claim that the weak forces are responsible for life's homochirality one would need to propose a mechanism *via* which this tiny difference could be amplified to give the observed imbalance in life forms.

If the inner chirality of atoms is insufficiently chiroselective, one might look for external chiral factors that could shift the balance between enantiomers in the "primordial soup". Circularly polarized photons or spin-polarized cosmic particles have been considered, especially those produced as a result of parity-breaking weak interactions (Lee & Yang, 1956). Particles whose electric vector spirals (clockwise or counterclockwise) along their direction of motion are chiral in the same sense that screws are right- or left-handed, and when they interact with matter, they are absorbed differently by different enantiomers. It was proposed that photons resulting from β-decay should be circularly polarized and could have a stereoselective effect on organic matter (Vester *et al.*, 1959). A number of experiments were performed to verify the Vester-Ulbricht hypothesis, leading to the conclusion that this was not an effective mechanism for creating a chiral imbalance. This was reviewed in (Bonner, 2000).

To conclude, the parity-breaking weak interactions would be the best natural candidate to explain the nonparity of biological molecules, were it not for the very large energy gap between the parity violating energy difference (PVED) and the energy regime of chemical interactions. An extensive perspective on the issue of parity violation in chiral molecules and its possible role in the emergence of biological homochirality was published recently (Quack *et al.*, 2022).

Probabilistic models rely on chance events. To explain the observed homochirality of biological molecules, the models require two components: an initial breaking of the balance between enantiomers (enantioselectivity), followed by an amplification of the initial imbalance (enantioenrichment). In this scenario, the initial imbalance stems from random fluctuations at the molecular level, followed by amplification *via* asymmetric autocatalysis in which a chiral molecule assists its self-production (Mislow, 2003). Such autocatalytic reactions have been investigated by Soai and coworkers (Soai *et al.*, 1995; Soai *et al.*, 1999). Once set in motion, these self-propelling reactions could amplify a small initial imbalance between the enantiomers. One scenario that was considered involved "isotope chirality", as the source of the initial imbalance. Isotope chirality is a result of ^{13}C substituting a ^{12}C atom in otherwise achiral organic compounds (Kawasaki *et al.*, 2009). The authors demonstrated that the presence of an isotope bestowed sufficient chirality on an achiral compound to set off enantioenrichment in an autocatalytic mechanism (Fig. 3). The question remains how to achieve the necessary initial imbalance between the "isotope enantiomers", even a tiny one, that could then be amplified. The isotope substitution in a molecule appears to be random and therefore expected to result in a 1:1 racemic mixture.

The Soai autocatalytic reaction, using an isotopically (^{13}C/^{12}C) chiral molecule as the initiator, was recently used to estimate the amount of energy needed to trigger enantioselectivity (Hawbaker & Blackmond, 2019). Multiple runs of the reaction were performed at various dilutions of the initiator to assess its threshold concentration sufficient to break the balance between the produced enantiomers. The threshold enantiomeric excess for the initiator was estimated to be between 1 and 0.1% of the initiator molecule. The authors then turned to stochastic simulations to estimate the amount of energy required to break the balance between the enantiomers under autocatalytic conditions and they obtained values between 1.5×10^{-7} and 1.5×10^{-8} kJmol^{-1}. This energy is five to seven orders of magnitude larger than the current estimates of PVED quoted in the previous section (Quack, 2002), confirming that the weak forces were unlikely to be the cause of biological homochirality. On the other hand, this symmetry-breaking energy threshold also is unlikely to be achieved by chance in the stochastic scenario. Thus, the probabilistic models also have a problem with delivering the necessary initial imbalance which could then be amplified *via* an autocatalytic chain reaction. Stochastic events tend to balance out, and if, by chance, an imbalance between enantiomers arises at some place, it is likely, that a compensating imbalance arises somewhere else. To circumvent this, the size of the "pool of the primordial soup" could be reduced, and then the number of possibilities would be reduced. Therefore, a fluctuation would have a better chance of not being canceled out by another fluctuation in the opposite direction. However, reducing the size of the pool

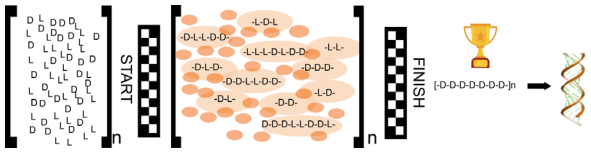

Figure 4. Chiroselective self-assembly leading to independently evolving "libraries" of polymers having different chiralities. As the populations evolve, they begin to differ. Eventually, homochiral "winner sequences" emerge from one of the libraries.

also reduces the chance of a significant fluctuation occurring in the first place.

Another approach to breaking the symmetry of the primordial racemic soup relies on the "chiroselective self-assembly" of nucleobase sequences. In this model, the chiral templates facilitate the synthesis of more oligomers of the same chirality. In time, the L- and D-libraries grow and evolve independently. Eventually, they diverge because the number of possibilities is greater than what is able to be obtained in the limited pool of resources. Eventually, "winner sequences" emerge in one of the libraries, having no symmetric equivalents in the other library (Fig. 4). Thus, homochiral seeds of biological molecules could arise (Bolli *et al.*, 1997).

CRYSTAL-BASED MODELS

Some of the proposed models for enantioselectivity and enhancement rely on crystallization. Crystals begin as seeds consisting of a small number of molecules and grow as regular lattices, often reaching macroscopic dimensions. Thus, crystallization can be considered a means to amplify interactions occurring at the molecular level up to the macroscopic scale. Due to its amplifying effect, crystallization is analogous to autocatalysis.

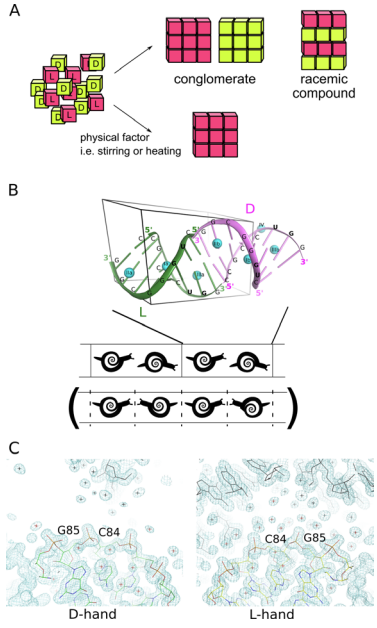

Figure 5. (A) When crystals grow from a solution of a racemate, they can be either racemic compounds (containing both enantiomers) or conglomerates (enantiomers form separate crystals). In specific cases, conglomerates can be nudged to homochirality by a physical factor (see text). (B) In racemic compounds, the enantiomers sometimes pack asymmetrically, which means that they can differ significantly in their structures and lattice contacts in the crystal (see Kiliszek *et al.*, 2021). (C) Section of electron density (*blue contours*) of the crystal structure reported by Kiliszek and others (Kiliszek *et al.*, 2021), showing asymmetry between the L- and D-RNA oligomers, with major differences in their interactions with the solvent and crystal lattice contacts.

A racemate can crystallize in two different ways, forming either separate crystals of L- and D-enantiomers ("conglomerates") or crystals containing both enantiomers ("racemic compounds") (Fig. 5A). In themselves, these crystals do not change the enantiomeric balance, but some mixtures of conglomerates can be nudged to homochirality by a physical factor, such as stirring or heating. This is possible under specific conditions. One condition is that the compound remaining in the liquid phase can undergo racemization, which enables the shifting of the balance between the L- and D-crystals (Kondepudi *et al.*, 1990). Another possibility exists for nonchiral molecules that can form chiral conglomerates (Viedma, 2005).

With racemic compounds, the main concept is that crystallization removes equal amounts of L- and D-molecules from the solution. Therefore, any initial imbalance in the quantities of the enantiomers is enhanced in the liquid phase (Klussmann *et al.*, 2006; Breslow & Levine, 2006). For this model to work, a preexisting imbalance, however small, is needed.

EXPERIMENTAL REPORTS

A number of research papers have been published that report on observations considered to be significant deviations from parity, with implications for the origin of biological homochirality. In a study published in 1999, crystals were grown from racemic solutions of sodium ammonium tartrate as well as chiral complexes of cobalt and iridium (Szabó-Nagy & Keszthelyi, 1999). The crystals were collected, dissolved and the optical activity of the resulting solution was analyzed, showing a chiral balance in the tartrate but an imbalance in the heavy metal compounds. This result indicated that from the balanced enantiomeric mixtures of the Ir and Co compounds, one enantiomer crystallized more easily than the other. This was interpreted as a sign of the parity-violating weak forces biasing the intermolecular interactions. The authors stated that "there is hope of detecting parity-violating energy difference in crystallization because macroscopic crystals consist of a large number of molecules". Further statistical analysis showed that the asymmetry of the Ir data was significant, while the effect for Co was inconclusive; thus, it could not be ruled out that the observed effect was due to other factors (Avalos *et al.*, 2000).

A paper from 2006 describes a study of L- and D-polypeptides in solution by means of circular dichroism (CD) and isothermal titration calorimetry (ITC) (Scolnik *et al.*, 2006). Subtle differences in the helix-coil transition energies of the different enantiomers were reported. The authors argued that the tiny effect of parity-violating interactions could be amplified in the cooperative process of helix formation. They also proposed that the *ortho* spin isomers of H_2O, having a magnetic field, could have a preference for interacting with the L-polypeptides due to their magnetic component induced by the weak forces. A related work from the same research group reported differences in solubility between L- and D-tyrosine, discerned by their rate of crystallization (Shinitzky *et al.*, 2002; Deamer *et al.*, 2007). The authors suggested this was due to the energy differences originating from parity violation. This was challenged by (Goldberg, 2008), who, having performed a series of crystallization experiments, concluded that the difference "is the result of a diastere-

omeric interaction between an airborne, non-racemic, chiral influence – probably a fungal spore – and the tyrosine enantiomers, enhancing the degree of crystal nucleation of D-tyrosine over L-tyrosine". Another critique came from (Lahav *et al.*, 2006), who repeated the crystallization experiments in their lab and observed that "samples provided by Shinitzky indeed displayed the effect he reported in his article, however, their results could not be repeated with samples obtained from other sources"; thus they concluded that the observed bias was most likely caused by impurities in the samples. In response to this, the Shinitzky group published "Comments in a Discussion", in which they acknowledged impurities as a major problem in their experiments aimed at pinpointing a very small effect (Shinitzky & Deamer, 2008). They concluded that it would be easier to look for any parity violating effects "in bulk phases, rather than in dynamic processes such as crystallization" and referenced papers reporting a Raman spectroscopic study of L- and D-RNA oligomers in solution (Bolik *et al.*, 2007) and a CD study of L- and D-polyglutamate undergoing temperature-dependent helix-coil transitions (Kodona *et al.*, 2008). The authors of both of these papers attributed the observed differences to parity-violating weak interactions.

A more recent report describes a study of crystalline D-alanine by means of Raman scattering and neutron powder diffraction (Belo *et al.*, 2018a). The authors claimed to have observed significant differences in the hydrogen bonding in comparison with L-alanine. Their results were challenged by (Bürgi & Macchi, 2018) who raised a number of methodological objections and then stated that "the conclusions drawn by Belo *et al.* are deemed inappropriate as the data presented do not contain sufficient information to reach such a conclusion". They added that the same objections also applied to the Raman spectroscopic study (see the paragraph above) of RNA oligomers (Bolik *et al.*, 2007). In response, Belo and others (Belo *et al.*, 2018b) denied that they had drawn any conclusions concerning the parity-violating energy difference in their original paper and added that "properties of L- and D-alanine, and the L- and D-amino acids in general, are a fascinating and important area of study for our understanding of nature, irrespective of whether they are related, or not, to the weak nuclear force and parity violation.".

A recent paper reported a crystal structure with clear differences between the L- and D-enantiomers of an RNA oligomer (Kiliszek *et al.*, 2021). The enantiomers assembled in the crystal in an asymmetric manner (Fig. 5B), made different lattice contacts and had different exposures to the water and metal ions present in the crystal (Fig. 5C). Crystals in which enantiomers are not constrained by crystallographic symmetry are known as kryptoracemates; these have been observed in small-molecule crystallography and represent *circa* 1% of structures in which enantiomers are cocrystallized (Clevers & Coquerel, 2020). These crystals could be relevant to the issue of biological enantioselectivity/deracemization because enantiomers exposed to different environments should have different stabilities. Consequently, different amounts of L- and D-molecules will remain after a certain time. Two types of such RNA-containing kryptoracemates were obtained, being mirror images of each other; therefore, in large volumes, their effects on the balance between the enantiomers should average out. However, in small volumes, with a small number of crystals, or perhaps just one crystal, the chances of a significant imbalance developing between enantiomers are greatly increased. The authors noted that this model required no initial imbalance between the enantiomers, as both enantioselection and enantioenrichment were included in the model; the crystal lattice provided a stable asymmetric environment for the enantiomers, while crystal growth amplified the effect up to the macroscopic scale.

Another recent paper describes the crystallization of ribo-aminooxazoline, an RNA precursor, on uniformly magnetized surfaces, demonstrating a significant enantioselective effect under some conditions (Ozturk *et al.*, 2023). The authors discuss possible scenarios of enantioenrichment occurring on the surface of magnetized sedimentary rocks on the prebiotic Earth. Small magnetite particles can sediment uniformly even in the Earth's weak magnetic field.

DISCUSSION

The formative events that defined life's basic characteristics, including the chirality of biological molecules, are shrouded in the distant past. We may never know exactly how life developed on Earth, but we can make informed retrospective speculations based on our knowledge of life's present form and the knowledge of universal mechanisms that govern life's processes. The natural candidate for tipping the balance of a racemic "primordial soup" toward homochirality would be the chiral weak force, but it appears that the energy it imparts on molecules is orders of magnitude less than what is needed for a significant effect on chemical processes. Chance fluctuations have larger amplitudes locally but tend to average out over space and time. We simply do not know an enantioselective process that would deliver a significant effect. Therefore, we need a massive amplification mechanism to turn any slight, innate or transient imbalance into a dominant form. One possibility is an autocatalytic process or rather some yet unknown "series of persistent chemical and physical processes that act synergistically and stepwise" (Hawbaker & Blackmond, 2019). The other possible means of "enantioenrichment" is crystallization. Two models contain both of the required steps of enantioselection and enantioenrichment: the evolutionary model of template-based "chiroselective self-assembly" (Bolli *et al.*, 1997) and the model based on the crystallization of kryptoracemates (Kiliszek *et al.*, 2021).

The deterministic and probabilistic models are different in nature but share a common aspect: both operate on an infinitesimal scale, meaning that the probability of a significant outcome of their action is also low. Chiral resolution (enantioselection) was an unlikely event. After the racemic balance was tipped, the initial small excess of one of the enantiomers was expanded (enantioenrichment) by one of the proposed mechanisms or by some other mechanism that remains unknown. Notably, however, such an expansion, even if significant, is still insufficient to explain the persistence of the enantiomeric imbalance over time. A lasting imbalance needs a mechanism to support it. Otherwise, the system will spontaneously return to thermodynamic equilibrium, while entropy is maximized. For instance, we can envision a scenario in which a minute initial excess of one enantiomer is greatly expanded by some autocatalytic mechanism. A significant imbalance appears, but there is no reason why a corresponding autocatalytic reaction should not also occur for the other enantiomer. At best, we can get a head start in multiplying one enantiomer before the symmetric process undermines the imbalance. The

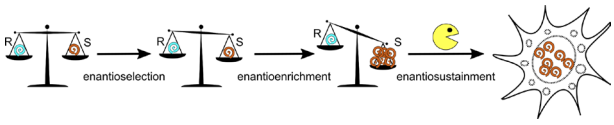

Figure 6. Result of enantioselection and enantioenrichment has to be sustained from returning to a thermodynamic equilibrium. Living organisms are well suited for maintaining a nonequilibrium thermodynamic state. It is probable that an enantioenriched solution evolved in or was engulfed by a primordial living organism or some other dissipative thermodynamic system, and thus it was stabilized.

likely result is the reestablishment of an equilibrium. To maintain an imbalance, a cascade of processes, such as the autocatalytic reaction is needed, and this is even less likely to occur than a single such event. An alternative way to maintain a thermodynamically unfavored state is to establish a lasting nonequilibrium thermodynamic system with a continuous flow of energy and matter. Life is such a system. Therefore, it is possible that the enantioselection and enantioenrichment were closely knit with the emergence of early life in which the imbalance was promptly embedded and has been sustained ever since (Fig. 6).

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